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Denosumab — a new option in the treatment of osteoporosis

Denosumab — nowa opcja w leczeniu osteoporozy

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Abstract

Denosumab is the international name of a human, monoclonal antibody approved for the treatment of osteoporosis. This antibody is associated with RANK ligand (RANKL), inactivating it. In consequence, the formation and survival of osteoclasts are suppressed, leading to their apoptosis. All this results in lower bone resorption, while bone mineral density (BMD) increases.

Denosumab also reduces the risk of vertebral and non-vertebral fractures. This agent is similarly effective in various stages of renal function impairment; it does not impair fracture healing processes nor contribute to atherosclerosis progression in patients with high cardiovascular risks. Following an analysis of adverse effects, performed in the FREEDOM study (in which it was demonstrated that the incidence of the majority of adverse effects observed in the course of denosumab use was similar to that in the placebo group), its safety for patients can definitely be confirmed. **(Pol J Endocrinol 2011; 62 (1): 79–83)**

Key words: *denosumab, RANK, RANKL, fractures*

Streszczenie

Denosumab to nazwa międzynarodowa ludzkiego, monoklonalnego przeciwciała, dopuszczonego do leczenia osteoporozy. Przeciwciało to wiąże się z ligandem RANK (RANKL), unieczynniając go. Na skutek tego dochodzi do zahamowania tworzenia się i przeżycia osteoklastów i do ich apoptozy. W wyniku tego zmniejsza się resorpcja kości, a co za tym idzie, zwiększa się ich gęstość mineralna (BMD, *bone mineral density*). Denosumab zmniejsza też ryzyko złamań kręgosłupa i złamań pozakręgowych. Lek ten jest podobnie skuteczny w różnych stadiach upośledzenia czynności nerek, nie upośledza gojenia się złamań i nie powoduje progresji miażdżycy u chorych wysokiego ryzyka sercowo-naczyniowego. Na podstawie analizy działań niepożądanych przeprowadzonych w badaniu FREEDOM (w którym wykazano, że częstość olbrzymiej większości występujących w trakcie jego stosowania objawów niepożądanych jest podobna jak w grupie placebo) można stwierdzić, że lek ten jest bezpieczny dla chorych. **(Endokrynol Pol 2011; 62 (1): 79–83)**

Słowa kluczowe: *denosumab, RANK, RANKL, złamania*

Introduction

Receptor-activator of nuclear factor κB, known as RANK, is the key factor stimulating the maturation, proliferation and fusion of preosteoclasts, as well as supporting the osteoclastic activity of mature osteoclasts and maintaining their survival. The RANK receptor is similar to the other receptors belonging to the so-called TNF receptor family, at least regarding the extracellular domain, the structure of which resembles that of the CD40 particle. However, the intracellular domain is not like any known receptors belonging to the TNF family.

Activation of the RANK receptor leads to activating intracellular signals, leading to the activation of various transcriptive factors, which, in turn, influence the expression of such genes as the calcitonin receptor gene, TRAP, CATK, integrin β, INF, NFAT2, myc, src and others. Their activation results in the stimulation of maturation and activities of osteoclasts, which, in effect, leads to bone mass loss, osteoporosis development and the occurrence of fractures [1, 2]. Osteoprotegerin (OPG, a bone-protecting substance), which can bind a RANKL particle, protects the system against these effects in physiological conditions, which makes the ligand-receptor binding impossible. OPG exerts a RANKL-opposing activity, thus protecting against osteoporosis.

The RANK/RANKL/OPG system also participates in the pathogenesis of many other diseases of the osteoarticular system, as set out in Table 1. The system seemingly plays a certain role in the pathogenesis of atherosclerosis. For example, mice with congenital deficits of osteoprotegerin develop vascular calcifications [4] and any interference in the RANK/RANKL/OPG system may reduce calcium deposition in the coronary vessels [5].

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Table I. *Diseases, the pathogenesis of which involves participation of the RANK/RANKL/OPG system*

Tabela I. *Choroby, w patogenezie których uczesticzy układ RANK/RANKL/OPG*

Metabolic diseases of bones
Paget's disease:
— sporadic (increased RANKL expression, an increased response of osteoclasts to RANK stimulation),
— familial (familial expansile osteolysis/familial Paget's disease
— RANK activating mutation)
— juvenile (juvenile Paget's disease
— OPG inactivating mutation)
Post-menopausal and secondary osteoporosis (e.g. in the course of hyperparathyroidism, glucocorticoid-induced)
Neoplasms
Multiple myeloma
Osteolytic metastases
Neoplastic hypercalcemia
Rheumatoid arthritis

So it is possible that osteoporosis and atherosclerosis, two very often comorbid diseases, may have a common pathogenetic basis [6].

As should be clear from the above statements, a pharmacological suppression of the RANK/RANKL/OPG system could reduce bone resorption.

Great expectations have been associated with such a treatment, namely that it may also decrease the incidence of fractures in patients with osteoporosis. The first attempts at such therapy were undertaken with the use of recombined osteoprotegerin, although this has yet to enter the stage of advanced clinical trials. It has now been replaced by an anitibody against RANKL.

This antibody has been launched onto the market under the international name of denosumab. It is a monoclonal, entirely human antibody of IgG2 type. Available literature data regarding its efficacy and safety is discussed below (Table I).

Denosumab's effects on fracture risk reduction

Fracture risk reduction is the most important end-point in all studies of medical agents used in the treatment of osteoporosis and the ultimate goal of anti-osteoporotic therapy.

The anti-fracture effect of denosumab was evaluated in the FREEDOM study, a randomised, double-blind, placebo-controlled clinical trial [14]. A total of 7,868 women were enrolled into the study, their ages varying between 60 and 90 years and their bone mineral density (BMD), measured as T-score of the hip and/or of the lumbar spine, within the range –2.5 to –4.0 SD. Vertebral fracture was diagnosed in 24% of the women at therapy onset. Prior three-year treatment with oral bisphosphonates (and, if its duration was shorter, at least 12 months were necessary from the last bisphosphonate administration to include such a patient), treatment with i.v. bisphosphonates, PTH, strontium, calcitonin, fluorides, glycocorticosteroids and other agents, which could have affected BMD during the six weeks before the start of our study, were the exclusion criteria. Various diseases, which could in any way affect bone metabolism, were also exclusion criteria. Calcium and vitamin D were supplemented in all the patients throughout the entire study duration.

After three years of the study, a significantly reduced fracture risk was observed in the patients treated with denosumab vs. the placebo group. The risk of fresh vertebral fracture decreased during that period by 68% ($p < 0.001$);during the first year the risk dropped by 61%, during the second year by 78% and during the third year by 68% ($p < 0.001$). During the three-year observation, the absolute fracture risk was 7.2% in the placebo-treated group as against only 2.3% in the denosumab-treated group.

The risk of clinically overt fracture decreased by 69%, and the risk of multiple fracture by 61%. In turn, the risk of non-vertebral fracture fell by 20% (the absolute risk was 6.5% in the denosumab-treated group and 8% in the placebo-treated group, $p = 0.01$) and the risk of hip fracture by 40% ($p = 0.04$). Kaplan-Meier curves which show the end-points are presented in Figure 1.

Denosumab effects on BMD and bone metabolism markers

These effects have been evaluated in several studies. In one, 412 women were enrolled, all post-menopausal and with low bone mineral density (BMD), measured by T score of the lumbar spine between –1.8 and –4.5 or T score of the femoral neck between –1.8 and –3.5. The patients were randomised into denosumab-treated groups, one with denosumab doses of 6, 14 or 30 mg every three months, the other with denosumab doses of 14, 60, 100 and 210 mg every six months, plus two control groups, in which either alendronate or a placebo was administered [7]. After a year of denosumab administration, a dose- and time-interval-dependent increase of spinal (3–6.7%) and total hip (1.9–3.6%) BMD was noted, together with a quick and reversible reduction of bone metabolism marker concentrations (e.g. CTX concentration was reduced by almost 90%).

The study was then extended by a subsequent 12 months [8]. BMD increase was continued during the second year, but its pace was slower. The total increase

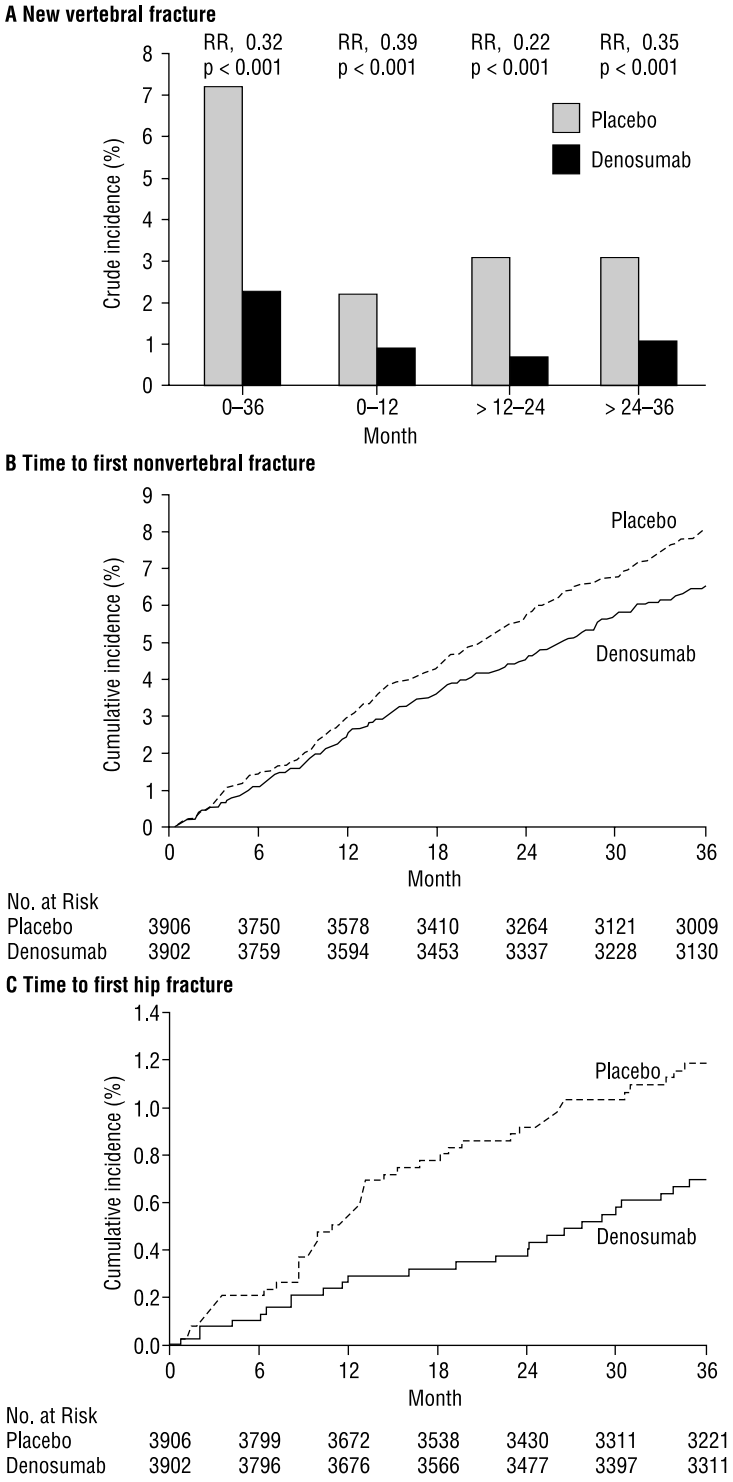

Figure 1. *Incidence of new vertebral, non-vertebral, and hip fractures. The primary end point was the incidence of new vertebral fractures at 36 months (**A**, left), which is shown for each study year (**A**, right). Risk ratios (RRs) are for subjects in the denosumab-receiving group, as compared with those receiving a placebo. Kaplan–Meier curves for the time period to the first non-vertebral fracture (**B**) and the first hip fracture (**C**) were determined on the basis of the subjects who did not have any fracture or who did not leave the study before the relevant time. The subjects at risk at 36 months included all those patients who completed the end-of-study visits at or after the start of the window for the 36-month visit. Reprinted from [14], with permission*

Rycina 1. *Występowanie nowych złamań kręgów, pozakręgowych i złamań biodra. Pierwotny punkt końcowy, którym było wystąpienie nowych złamań kręgów oceniano po 36 miesiącach leczenia, pokazano w części **A** (lewa strona), to samo po każdym roku leczenia (słupki po prawej). Ryzyko względne (RR) oceniano dla chorych leczonych denosumabem, w porównaniu z tymi, którzy otrzymywali placebo. Krzywe Kaplana-Meiera dotyczące czasu do wystąpienia pierwszego złamania pozakręgowego (**B**) i pierwszego złamania biodra (**C**) oceniano w odniesieniu do osób, które nie miały żadnego złamania ani nie opuściły badania przed właściwym czasem. Liczba chorych (No. at Risk) w 36 miesiącu dotyczący tych pacjentów, którzy odbyli wizytę końcową w lub po zakończeniu „okienka czasowego" przewidywanego dla wizyty w 36. miesiącu. Przedrukowano za zgodą z: [14]*

(after 24 months) of spinal BMD vs. the pre-treatment values was 4.13–8.89% (depending on the applied dose of the drug). The suppression of bone metabolism markers was maintained throughout the study period.

The obtained results suggest that 60 mg of denosumab, administered every six months, was an optimal therapeutic protocol. In that situation, the patients who had completed the study (and agreed to its continuation) were divided into groups [9]. In one, the treatment with denosumab at a dose of 60 mg every six months was continued; in a second group, the therapy was withdrawn for 12 months, then recommenced; while in the third group, the therapy was permanently terminated. Patients who had originally received a placebo continued to do so, while the patients treated with alendronate did not continue to receive that drug. Those treatment protocols were continued for two years. The patients treated with denosumab demonstrated further BMD increase (e.g. in lumbar spine by 9.4–11.8% vs. the base values) and the concentrations of bone turnover markers remained low during the entire study period. Denosumab withdrawal decreased BMD values and increased bone turnover marker concentrations, which, however, returned to the values before therapy withdrawal in the group of women in whom the treatment was restarted [9].

Denosumab effects on BMD and bone turnover markers were evaluated also in women with osteopenia. After two years of treatment with denosumab at a dose of 60 mg every six months, spinal BMD increased by 6.5% vs. the base values. A significant increase of BMD was also observed in the hip, the radial bone and the total body. Bone turnover marker concentrations in serum demonstrated a significant drop, e.g. the mean reduction of CTX concentration was almost 90% [10].

A comparison of the effects of denosumab and alendronate on BMD and bone turnover markers and an evaluation of sequential administration of these two drugs

Apart from the above-mentioned phase II study, where alendronate was administered in one of the control groups, two other studies were performed evaluating alendronate and denosumab.

In one, a 12-month therapy resulted in BMD increase, higher by approximately 1% in patients treated with denosumab vs. those treated with alendronate (spinal BMD by 1.1%, hip BMD by 0.9% and radial bone shaft BMD by 0.6%). The reduction of bone turnover marker concentrations in serum was greater in the patients treated with denosumab [11].

In the other study, a sequential treatment was evaluated (a switch from alendronate to denosumab). Here also, a significantly higher increase of BMD was observed, with a simultaneously larger drop of bone turnover marker concentrations in the patients switched to denosumab treatment vs. those who continued alendronate administration [12].

In these studies comparing denosumab to alendronate, the preferences of patients were also evaluated. More than 60% of the patients prefer denosumab treatment, with subcutaneous administration once every six months, less than 20% prefer an alendronate tablet once a week, and also less than 20% have no preferences at all [13]. These results are not surprising in that they follow the general tendency of patients towards medical treatment with drugs which allow for longer intervals between subsequent doses.

Additional analyses of data from the FREEDOM study

To date, a few additional analyses have been performed of data from the FREEDOM study; thus far, the data has been published as conference abstracts, briefly discussed below:

Denosumab in patients at high fracture risk

In an analysis comparing various subpopulations at high fracture risk with other patients (e.g. women aged over 75, women with vertebral fractures present at the time of randomisation vs. women without such fractures, as well as women with a few concomitant fracture risk factors vs. other patients), it was demonstrated that, in the majority of those subpopulations, denosumab was effective, both in the patients at lower, and those at higher, fracture risk. The only exception was a similar effectiveness of denosumab in reducing non-vertebral fractures of women with a T score of the femoral neck higher or lower than –2.5 [15].

Denosumab in patients with impaired renal function

Denosumab's effects have been evaluated regarding BMD and risk reduction of fresh vertebral fractures, depending on renal function, measured as the estimated glomerular filtration rate (eGFR) from creatinine concentration, following the Cockroft-Gault formula [16].

No significant differences were found in denosumab activity in the groups of patients with eGFR > 90 ml/min, 60–89 ml/min, 30–59 ml/min and 15–29 ml/min. It should, however, be mentioned that the small number of patients in the last group, i.e. patients with highly impaired renal function, reduces the value of the obtained result.

Denosumab's effects on the development of vascular calcifications

An analysis evaluated aortal calcifications during the study duration in 2,363 women at high cardiovascular risk. Aortal calcification was assessed in a 24-degree scale, according to lateral spinal images, taken in conformity with the FREEDOM study protocol. The results of that analysis did not reveal any difference in the progression of aortal calcifications between the group of patients treated with denosumab and the placebo group [17]. So it seems that the drug does not increase atherosclerosis progression in such patients.

Denosumab and fracture healing

Also in that analysis, non-vertebral fracture healing complications were evaluated and, in a small population of patients with antebrachial fractures (distal part of the radial bone), serial X-ray images were taken of the fracture site. Neither any disturbances nor delays in fracture healing were found in the group treated with denosumab *vs.* the placebo group [18].

Adverse effects

The adverse effects of denosumab are best evaluated on the basis of a FREEDOM study analysis, in which their incidence rates were evaluated in the largest group of patients, both after the medication and after a placebo. The effects occurred with similar prevalence in both studied groups. In the patients treated with denosumab, cutaneous changes and meteorisms were more frequently observed, as well as hypodermitis, while falls and cerebral concussions were seldom recorded. The prevalence of other adverse effects did not significantly differ in either group. Neither were any differences observed in the prevalence of severe adverse effects, the prevalence of symptoms leading to treatment withdrawal, nor the prevalence of infections. It appears from this analysis that denosumab is a medicinal product safe for use by patients [19].

Summary

Denosumab is a safe and effective medicinal agent, approved for the treatment of osteoporosis [16].

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